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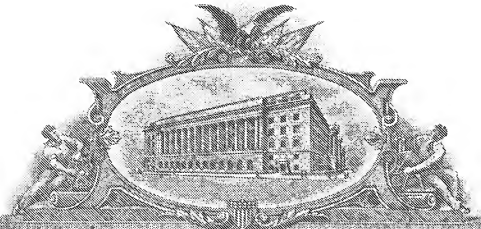

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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)

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Additional inventors are being named on the _____ *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

PROCESS FOR THE MANUFACTURE OF LYSERGIC ACID

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 11 ☐ CD(s), Number _____

☐ Drawing(s) *Number of Sheets* _____ ☐ Other (specify) _____

☐ Application Data Sheet. See 37 CFR 1.76

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Respectfully submitted,

SIGNATURE Dennis A. Emma

Date February 20, 2004

REGISTRATION NO. 50980 *(if appropriate)*

Docket Number: GAL0020-P-USA

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Ladislav Cvak and Vlastislav Mojczek
Serial Number:	To be assigned
Filing Date:	HEREWITH
Title:	PROCESS FOR THE MANUFACTURE OF LYSERGIC ACID
Attorney Docket No.:	GAL0019-P-USA

CERTIFICATION UNDER 37 C.F.R. § 1.10

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Dear Sir:

Enclosed herewith for filing with the United States Patent and Trademark Office in the above-identified Provisional Patent Application pursuant to 37 C.F.R. § 1.53 (c) are the following documents:

1. Provisional Application Cover Sheet (one page);
2. Provisional Patent Application (11 pages); and
3. Return Postcard.

Respectfully Submitted,

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PROCESS FOR THE MANUFACTURE OF LYSERGIC ACID

Inventors: Ladislav Cvak and Vlastislav Mojczek
(Attorney Docket Number GAL0019-P-USA)

FIELD OF THE INVENTION

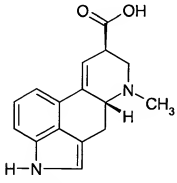
[0001] The present invention relates to a process for the manufacture of lysergic acid by isomerizing paspalic acid in high yield.

BACKGROUND OF THE INVENTION

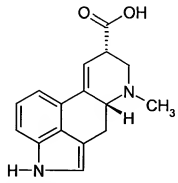
[0002] Lysergic acid is a basic structural part of natural ergot alkaloids. It is manufactured in large scale as an intermediate for the synthesis of several semisynthetic ergot alkaloids, which have found uses as drugs, *e.g.*, ergometrine, methylergometrine, methysergide and nicergoline.

[0003] Paspalic acid is also an ergot alkaloid, which is readily available by fermentation. The conversion of paspalic acid to lysergic acid is known by various methods. The process, however, results in the formation of unwanted impurities such as the epimer, isolysergic acid, when known isomerization techniques are used.

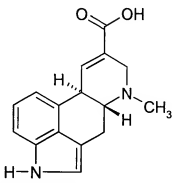
[0004] Lysergic acid, paspalic acid and isolysergic acid are natural chiral compounds with the *R* configuration on the chiral center in position 5 of their skeleton. As used herein, lysergic acid, isolysergic acid and paspalic acid mean d-lysergic acid, d-isolysergic acid and d-paspalic acid. Their structures are depicted below.



d-lysergic acid



d-isolysergic acid



d-paspalic acid

[0005] Lysergic acid is typically manufactured by hydrolyzing natural ergot alkaloids like ergotamine or ergotoxine isolated from ergot. Another typical preparation involves the partial synthesis from natural precursors which are available by fermentation, such as by the hydrolysis of lysergic acid hydroxy-ethylamide or the isomerization of paspalic acid.

[0006] Paspalic acid and its isomerization to lysergic acid was first described by Kobel (Helv. Chim. Acta 47:1052 (1964)). The isomerization was accomplished by boiling paspalic acid in diluted aqueous sodium hydroxide. When the isomerization of paspalic acid was carried out by this procedure, however, the conversion to lysergic acid was unsatisfactory (more than 5% of paspalic acid remained in the reaction mixture) and the high temperature used caused significant decomposition of the product. Similar results were obtained with other procedures described by Kobel *at al.* (Helv. Chim. Acta 64:478 (1981) and JP 70013302), both using isomerization in boiling aqueous potassium hydroxide. Moreover, the reaction mixture contained a significant amount of isolysergic acid (more than 25 %) which decreased both the yield and the quality of the resulting lysergic acid (the isolated lysergic acid contained about 5 % of isolysergic acid). Therefore further purification of the product was necessary. Another drawback was the low concentration of paspalic acid in the reaction mixture, which in turn required a large volume reactor.

[0007] Recently a new process of preparing lysergic acid was disclosed which described the use of aqueous tetraalkylammonium hydroxides to isomerize paspalic acid. (U.S. Patent No. 6,242,603). The reported yield of isolated lysergic acid containing about 3 % of isolysergic acid was about 80 %. The content of paspalic acid in the product was not disclosed. This reference also described the preparation of lysergic acid by above-mentioned process including isomerization in boiling diluted sodium or potassium hydroxide. These comparative examples describe the formation of lysergic acid in less than 60% yields.

SUMMARY OF THE DISCLOSURE

[0008] An advantage of the present invention is a facile method of preparing lysergic acid from paspalic acid in high yields and quality.

[0009] These and other advantages are satisfied, at least in part, by a process for the manufacture of lysergic acid which includes isomerization of paspalic acid by a concentrated

aqueous solution of sodium or potassium hydroxide. The process can advantageously be carried out within a few hours and at relatively low temperature. Isolation of essentially pure lysergic acid can be achieved in yields of greater than 70 % and containing less than about 1 wt % of paspalic acid and less than about 1 wt % of isolysergic acid. The process can additionally provide epimerization of any unwanted isolysergic acid to the desired lysergic acid.

[0010] Embodiments of the present invention include combining paspalic acid, water and a metal hydroxide, *e.g.*, potassium or sodium hydroxide, for a sufficient time to form lysergic acid, wherein the amount of the paspalic acid and metal hydroxide is in sufficient quantity to cause a phase separated reaction mixture. Additional embodiments include acidifying the reaction mixture after isomerization to form a lysergic acid salt; extracting lysergic acid from the salt with a mixture of methanol and aqueous ammonia; partial evaporation of the extract, crystallizing the extracted lysergic acid in a crystallization medium; separating the crystalline lysergic acid from its crystallization medium; washing the crystalline lysergic acid with water and methanol; and combining the crystallization medium and the washing solvent with additional paspalic acid, water, and a metal hydroxide to manufacture additional lysergic acid in high yield and quality.

[0011] Additional advantages of the present invention will become readily apparent to those skilled in this art from the following detailed description, wherein only the preferred embodiment of the invention is shown and described, simply by way of illustration of the best mode contemplated of carrying out the invention. As will be realized, the invention is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the invention. Accordingly, the descriptions are to be regarded as illustrative in nature, and not as restrictive.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0012] After experimentation and investigation, it was discovered that paspalic acid can be isomerized to lysergic acid by concentrated aqueous solutions of metal hydroxides in surprisingly high yield and quality. In particular, it was discovered that the use of

concentrated aqueous solutions of a metal hydroxide, e.g., sodium or potassium hydroxide, had positive effects on both the yield and the quality of the formed lysergic acid. Both, the yield and quality of the isolated lysergic acid were substantially better than that known to the art e.g. described in U. S. Patent 6,242,603 B1.

[0013] Based upon experimentation, it was discovered that when a sufficient amount of paspalic acid is dissolved in least about a 12 weight percent aqueous sodium or potassium hydroxide solution, a phase separated reaction mixture forms. Without being bound by any theory, it is believed that the phase separated reaction mixture provides an excellent medium for isomerizing of paspalic acid. Paspalic acid can be converted to lysergic acid in such phase separated medium under relatively mild conditions, e.g., after about 4 hours of mixing at a temperature of about 50 °C. Under these reaction conditions, the conversion of paspalic acid was greater than 98 % so that the reaction mixture contained less than about 2.0 % of paspalic acid and a balance concentration of isolysergic acid was about 18 % (both determined by HPLC).

[0014] In general, the present invention is practiced by combining paspalic acid, water and a metal hydroxide. Because of convenience, the paspalic acid is typically added to the aqueous solution of the metal hydroxide. In one aspect of the present invention, the ingredients, paspalic acid, water, and a metal hydroxide are combined in such quantity that a phase separated reaction mixture is formed. The ingredients are combined and, optionally, agitated for a time sufficient to achieve high conversion to lysergic acid. The temperature of the mixture can also be increased to the reaction rate up to the reflux temperature nevertheless the temperature between about 40 °C to about 60 °C was found out to be optimal. The temperature above this range can also deleteriously decompose the formed lysergic acid.

[0015] After formation, lysergic acid can be separated from the reaction mixture. In one embodiment for practicing the present invention, lysergic acid is separated from the reaction mixture by acidification, e.g., with sulfuric acid, to form a salt, which is more readily separated from the reaction mixture. For example, acidifying the reaction mixture to a pH below about 4.0 with sulphuric acid forms lysergic acid sulfate salt which precipitates from the reaction mixture and can then be readily collected by filtration. Experiments have shown that the crude salt contains roughly the same proportion of lysergic acid and isolysergic acid

formed by isomerizing of paspalic acid. Hence, it may be desired to further isolate the formed lysergic acid from its epimer.

[0016] In another aspect of the present invention, the process includes dissolving the crude lysergic acid salt in a mixture of methanol and aqueous ammonia to regenerate lysergic acid from its salt. This can be followed by crystallization of the lysergic acid which can be advantageously carried out by evaporating the ammonia and partial evaporation of the methanol from the solution and cooling the solution. After separating the crystalline lysergic acid from its crystallization medium in this example, it was found that the obtained crystalline lysergic acid contained less than about 10% of isolysergic acid. The content of this epimer can be further decreased by washing the crystalline lysergic acid with methanol.

[0017] In practising another aspect of the present invention, lysergic acid containing isolysergic acid impurity can be purified by washing crystalline lysergic acid with methanol to reduce the amount of isolysergic acid impurity to less than about 3 wt%. In practice, lysergic acid containing less than 1% of isolysergic acid can be finally obtained. It is believed that isolysergic acid is more readily dissolved in methanol that lysergic acid and that washing the desired product with methanol provides a convenient way to further purify lysergic acid.

[0018] Experimentation has shown that the mother liquors from the crystallization and washing steps contain mainly isolysergic acid. These solutions can be returned back to the process of isomerization, where the isolysergic acid is epimerized to the desired lysergic acid thus increasing the overall yield of a multi-batch or continuous process. This process, including the recycling of the mother liquors, was repeated up to ten times without any problems with the quality of the obtained product. Total yield of a multi-batch process, including the recycling of the mother liquors containing isolysergic acid, was up to about 90% and the quality of obtained lysergic acid was very high. For example, the average content of the main impurities, paspalic acid and isolysergic acid, was below about 1% individually.

[0019] Through experimentation it was found, no significant difference between the use of sodium or potassium hydroxides. Both hydroxides form a two-phase system when at least about one weight part of paspalic acid is dissolved in no more than about 20 weight parts of an aqueous solution containing at least about one weight part of sodium or potassium

hydroxides in 8 weight parts of water. Other metal hydroxides are believed useable in similar amounts, nevertheless because the use of other hydroxides is lacking the practical sense, it was not further investigated.

[0020] The following examples illustrate, but do not limit, the process. While the first example describes the first isomerization of paspalic acid so that it did not include any recycled material, the second example describes a typical manufacturing process where the mother liquors from a previous batch are returned to the next batch.

EXAMPLES

Example 1

The preparation of lysergic acid by a process which does not include recycling the mother liquors after crystallization of lysergic acid was achieved as follows:

100.0 g of paspalic acid (titration assay 98.5 %) was dissolved in 1000 ml of 5 % aqueous sodium hydroxide and then 150 g of sodium hydroxide was added to the solution. A formation of two-phase system was observed. The obtained two-phase system was then mixed for about 4 hours at about 50 °C under nitrogen. Then the reaction mixture was diluted with 1000 ml of water, cooled to 10 °C and acidified to a pH of about 3.5 with 40% sulfuric acid. A suspension of crystalline lysergic acid sulfate formed was then mixed for about 2 hours at about 5 °C. Then the crystalline lysergic acid sulfate was filtered off. The lysergic acid sulfate was extracted three times with a 500 ml of mixture of methanol and aqueous ammonia 95:5 (v/v) and the joined extracts were evaporated to about 200 grams, diluted with 200 ml water and left to crystallize at about 5 °C for 24 hours. The crystalline lysergic acid was then separated and washed by about 100 ml of water and three times with about 100 ml of methanol. After vacuum drying (24 hours at 60 °C and 30 mbar), 73.4 grams of lysergic acid was obtained (titration assay 99.1 %, content of paspalic acid 0.5 %, content of isolysergic acid 0.8 %). The mother liquors after crystallization of lysergic acid and the methanol solution obtained after washing the crystalline product were evaporated to a volume of about 200 ml and were then added to the next batch, Example 2.

Example 2

The manufacture of lysergic acid in greater than about 90% yield was achieved by adding the mother liquors from the previous batch (Example 1) to the isomerisation process as follows: About 50 grams of sodium hydroxide was dissolved in about 800 ml of water and 200 ml of the concentrated mother liquors from the Example 1. 100.0 grams of paspalic acid (titration assay 98.5 %) and finally 150 g of sodium hydroxide were added to the solution. A two-phase reaction mixture was subsequently formed. The obtained two-phase system was mixed for about 4 hours at about 50 °C under nitrogen. Then the reaction mixture was diluted with 1000 ml of water, cooled to 10 °C and acidified to about pH 3.5 with 40% sulfuric acid. The obtained suspension was mixed for 2 hours at about 5 °C and then crystalline lysergic acid sulfate was filtered off. The lysergic acid sulfate was extracted three times with 500 ml of mixture of methanol and aqueous ammonia 95:5 (v/v) and the joined extracts were evaporated to about 200 grams, diluted with 200 ml water and let to crystallize at about 5 °C for 24 hours. The crystalline lysergic acid was then separated and washed by 100 ml of water and three times with 100 ml of methanol. After vacuum drying (24 hours at 60 °C and 30 mbar), 90.8 grams of lysergic acid was obtained (titration assay 98.7 %, content of paspalic acid 0.6 %, content of isolysergic acid 0.9 %). The mother liquors after crystallization of lysergic acid and the methanol solution obtained after washing of the crystalline product were evaporated to a volume of about 200 ml and were added to the next batch.

In this disclosure there is described only the preferred embodiments of the invention and but a few examples of its versatility. It is to be understood that the invention is capable of use in various other combinations and environments and is capable of changes or modifications within the scope of the inventive concept as expressed herein.

What is Claimed Is:

1. A process for the manufacture of lysergic acid by isomerization of paspalic acid, in which the isomerization is brought about by a phase separated system comprising paspalic acid and an aqueous solution of sodium hydroxide or potassium hydroxide.

2. A process according to claim 1, in which at least about one weight part of paspalic acid is dissolved in about 20 weight parts of the aqueous solution of sodium hydroxide or potassium hydroxide.

3. A process according to claims 1 and 2, in which the aqueous solution of sodium hydroxide or potassium hydroxide is prepared by dissolving at least about one weight part of sodium hydroxide or potassium hydroxide in about eight parts of water.

4. A process according to claim 1, in which the isomerization is performed at the temperature in the range from about 20 °C to about 100 °C.

5. A process according to claim 1, in which the isomerization is performed at the temperature from about 40 °C to about 60°C.

6. The process of claim 1 wherein the lysergic acid is manufactured in a yield of no less than 70%.

7. A process according to claim 1, comprising crystallizing the lysergic acid from water or methanol or their mixtures and recycling the mother liquors back to the isomerization process.

8. A process for the manufacture of lysergic acid, the process comprising combining paspalic acid, water, and a metal hydroxide to manufacture lysergic acid, wherein the paspalic acid and metal hydroxide are in sufficient quantity to cause a phase separated reaction mixture.

9. The process of claim 8 further comprising acidifying the reaction mixture after isomerization to form crystalline salt of lysergic acid.

10. The process of the claim 9 wherein the acidification is accomplished by sulphuric acid.

11. The process of the claim 9 further comprising extracting lysergic acid from the lysergic acid salt by a mixture of methanol and aqueous ammonia to form a lysergic acid solution.

12. The process of the claim 11 further comprising partial evaporating of the lysergic acid solution and crystallizing lysergic acid.

13. The process of the claim 12 further comprising separating the crystalline lysergic acid from the crystallization medium and washing the crystalline product with methanol.

14. The process of claim 13 further comprising combining the crystallization medium and washing methanol with additional paspalic acid, water, and a metal hydroxide to form additional lysergic acid.

15. The process of claim 13 wherein the separated crystallized lysergic acid contains less than about 1 wt % of paspalic acid and less than about 1 wt % of isolysergic acid.

16. A process of purifying lysergic acid, containing isolysergic acid impurity, the process comprising washing crystalline lysergic acid with methanol to reduce the amount of isolysergic acid impurity to less than about 3 wt %.

17. The process of claim 16 comprising washing crystalline lysergic acid with methanol to reduce the amount of lysergic acid impurity to less than about 1 wt %.

ABSTRACT

Lysergic acid is formed in high yields and quality by isomerizing paspalic acid in a phase separated system formed by paspalic acid and concentrated aqueous metal hydroxide solution.